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U-Curve Relationship Between Orthostatic Blood Pressure Change and Silent Cerebrovascular Disease in Elderly Hypertensives

Orthostatic Hypertension as a New Cardiovascular Risk Factor

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OBJECTIVES The study investigated the clinical significance and mechanism of orthostatic blood pressure (BP) dysregulation in elderly hypertensive patients.

BACKGROUND Although orthostatic hypotension (OHYPO), often found in elderly hypertensive patients, has been recognized as a risk factor for syncope and cardiovascular disease, both the clinical significance and the mechanism of orthostatic hypertension (OHT) remain unclear.

METHODS We performed a head-up tilting test and brain magnetic resonance imaging (MRI) in 241 elderly subjects with sustained hypertension as indicated by ambulatory BP monitoring. We classified the patients into an OHT group with orthostatic increase of systolic blood pressure (SBP) of ≥20 mm Hg (n = 26), an OHYPO group with orthostatic SBP decrease of ≥20 mm Hg (n = 23), and a normal group with neither of these two patterns (n = 192).

RESULTS Silent cerebral infarcts were more common in the OHT (3.4/person, $p < 0.0001$) and OHYPO groups (2.7/person, $p = 0.04$) than in the normal group (1.4/person). Morning SBP was higher in the OHT group than in the normal group (159 vs. 149 mm Hg, $p = 0.007$), while there were no significant differences of these ambulatory BPs between the two groups during other periods. The OHT (21 mm Hg, $p < 0.0001$) and OHYPO (20 mm Hg, $p = 0.01$) groups had higher BP variability (standard deviation of awake SBP) than the normal group (17 mm Hg). The associations between orthostatic BP change and silent cerebrovascular disease remained significant after controlling for confounders, including ambulatory BP. The orthostatic BP increase was selectively abolished by alpha-adrenergic blocking, indicating that alpha-adrenergic activity is the predominant pathophysiologic mechanism of OHT.

CONCLUSIONS Silent cerebrovascular disease is advanced in elderly hypertensives having OHT. Elderly hypertensives with OHT or OHYPO may have an elevated risk of developing hypertensive cerebrovascular disease. (J Am Coll Cardiol 2002;40:133–41) © 2002 by the American College of Cardiology Foundation

In normal subjects, because of an autoregulatory mechanism, the blood pressure (BP) shows minimal variation with posture-dependent changes. In most hypertensive patients without autonomic nervous dysfunction, the postural BP changes are also minimal. Orthostatic hypotension (OHYPO), often found in elderly hypertensives, is well recognized as a risk for falls, syncope and cardiovascular events (1–4). In contrast, there have been few reports on orthostatic hypertension (OHT), in which the BP increases with orthostatic postural change (5–9). Although two previous reports suggested that an orthostatic BP increase predicts an increased risk of developing coronary artery disease (CAD) (5,7), the clinical significance and mechanism of OHT remain unclear.

We performed a head-up tilting test (HUT), ambulatory blood pressure monitoring (ABPM) and brain magnetic resonance imaging (MRI), which is the most sensitive method of detecting silent cerebrovascular disease, in 241 asymptomatic elderly hypertensives.

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METHODS

Patients. We initially enrolled 244 elderly hypertensive outpatients (age ≥60 years) who satisfied the following criteria: 1) essential hypertension with average clinic BP (measured within one week before ABPM by standard cuff methods after resting for at least 5 min while seated) on ≥2 occasions at separate visits >140 mm Hg for systolic blood pressure (SBP) and/or ≥90 mm Hg for diastolic blood pressure (DBP); and 2) average 24-h SBP ≥130 mm Hg or DBP ≥80 mm Hg (10). Thus, patients with white-coat hypertension were excluded (10); previous research showed that the prevalence of silent cerebral infarct (SCI) and risk of stroke in white-coat hypertensives are comparable to those in normotensives (11–13). These patients were enrolled from the three participating clinics between April 1996 and August 2000, and 188 patients in the present study were included in our previous study (13,14). No patient had received any antihypertensive medication for at

Abbreviations and Acronyms

ABPM	= ambulatory blood pressure monitoring
BP	= blood pressure
CAD	= coronary artery disease
DBP	= diastolic blood pressure
DWM	= deep white matter
ECG-LVH	= electrocardiographically verified left ventricular hypertrophy
HUT	= head-up tilting test
MRI	= magnetic resonance imaging
OHYPO	= orthostatic hypotension
OHT	= orthostatic hypertension
ONT	= orthostatic normotension
OR	= odds ratio
PR	= pulse rate
RR	= relative risk
SBP	= systolic blood pressure
SCI	= silent cerebral infarct

least 14 days before the study. After physical and laboratory examinations, we excluded patients with renal failure (serum creatinine level >130 mmol/l), hepatic damage present illness, or a past history of coronary artery disease (CAD) stroke, congestive heart failure, arrhythmia or other serious medical conditions. Patients with symptomatic OHYPO with SBP decrease >30 mm Hg 1 min after active standing, and those with possible diabetes mellitus (fasting glucose >5.5 mmol/l and/or hemoglobin A_{1c} >6.0%), were also excluded. This study was approved by the Research Ethics Committee, Department of Cardiology, Jichi Medical School, and informed consent was obtained from each subject.

The body mass index was calculated as weight (kg)/height $(m)^2$. Electrocardiographically verified left ventricular hypertrophy (ECG-LVH) was defined by abnormally high voltages of QRS complexes (RV_5 + SV_1 ≥3.5 mV) associated either with flat T waves (<10% of R) or with ST-segment depression and biphasic T waves.

HUT and definition of OHT and OHYPO. After BP and pulse rate (PR) were measured with an interval of 1 min at baseline and after the subjects had been in a supine position for at least 10 min, they were positioned upright on a tilt table at an angle of 70° for 15 min. Three patients who developed presyncope during HUT were excluded from this study, and the remaining 241 patients were studied further.

Orthostatic BP and PR changes were calculated as: the average during 6 to 10 min during tilting minus the average in the supine position during the 1 to 5 min just before the tilting (9). We classified the patients into an OHT group with orthostatic SBP increase ≥20 mm Hg (n = 26), an OHYPO group with orthostatic SBP decrease ≥20 mm Hg (n = 23) and an orthostatic normotension group (ONT) with neither of these two patterns (n = 192).

ABPM. After HUT, ABPM was carried out on a weekday with an automatic ABPM device employing the oscillometric method (ABPM-6307s, NipponColin, Komaki, Japan; TM-2421, TM-2425, A&D, Tokyo, Japan); this device recorded BP and PR every 30 min for 24 h. Based on each patient's diary, sleep BP was defined as the average BP from the time when the patient went to bed until the time he or she got out of bed, and awake BP as the average of BPs during the remainder of the day. The standard deviation of awake BPs of each patient was calculated. Morning BP was defined as the average BP during 2 h (4 to 5 points) after the time of awakening.

Brain MRI. Brain MRI was performed using a superconducting magnet with a main strength of 1.5 T (Toshiba MRT200FXII, Toshiba; SIGNA Horizon Ver. 5.8, General Electric, Vision, Siemens) within three months before or after ABPM. The T1- and T2-weighted images were obtained in the transverse plane with 7.8- to 8.0-mm-thick sections. The MRI images of the subjects were randomly stored and interpreted blind to the subjects' names and characteristics, as reported previously (13,14), and they were evaluated for subcortical infarcts and deep white matter (DWM) lesions. An SCI was defined as a low-signal-intensity area (3 to 15 mm) on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images (11–14). Multiple SCIs were defined as ≥3 infarcts/person. Advanced DWM lesion was defined as detection of hyperintense multiple punctate lesions or such lesions at the early confluent stage or those that had reached confluency in the DWM area on T2-weighted images.

Neurohumoral factors. Blood collection was performed after 10 min in the supine position just before the tilting, and after 15-min of tilting in 87 consecutive patients enrolled between June 1, 1996, and July 1998. All of these patients were included in the entire study population (n = 241) (Table 1). Blood samples were immediately centrifuged at 3,000 rpm for 15 min, and plasma was decanted and stored at −80°C until analysis. Catecholamines were measured with high-pressure liquid chromatography (Hitachi, Tokyo, Japan). Plasma renin activity was determined using a radioimmunoassay for angiotensin-I (PRA-SRL; SRL, Tokyo, Japan). Vasopressin was determined using a competitive radioimmunoassay (Mitsubishi Kagaku, Tokyo, Japan). All these assays were performed at the Special Reference Laboratory (Tokyo, Japan), and the intra-/intercoefficient of variation was 0.81% 2.2% for the norepinephrine assay, 0.85%/2.1% for the epinephrine assay, 6.8%/6.6% for the renin activity assay and 1.7%/3.9% for the vasopressin assay.

Reproducibility of OHT and alpha-adrenergic blocking effect. To investigate the reproducibility of OHT and the role of alpha-adrenergic activity in the mechanism of OHT, we administered selective $alpha_1$-blocker to the 55 hypertensives without OHYPO diagnosed by the first HUT. The patients for this substudy were enrolled between June 1, 1996, and July 1998, and all the initial baseline data of these patients were also included in the entire study data (n = 241) (Table 1) After the first ABPM and HUT, each patient was studied for a maximum of 11 weeks, with an observation period of three to five weeks, a titration period

Table 1. Clinical and BP Characteristics

Characteristics	Orthostatic Hypertension (n = 26)	Normal Group (n = 192)	Orthostatic Hypotension (n = 23)
Age (yrs)	75 (5.5)†	71 (6.5)	72 (6.2)
Male (%)	42	44	39
Body mass index (kg/m^2)	22.9 (3.9)	23.6 (3.3)	22.9 (2.8)
Current smoker (%)	38	21	30
Hyperlipidemia (%)	23	20	30
Duration of hypertension (yrs)	6.5 (6.6)	6.4 (7.0)	7.9 (8.9)
Previous antihypertensive medication (%)	27	46	43
ECG-LVH (%)	46†	23	43
Clinic SBP (mm Hg)	165 (23)	159 (17)	166 (19)
Clinic DBP (mm Hg)	93 (17)	90 (14)	91 (12)
PR (beats/min)	76 (14)	75 (11)	70 (10)
Head-up tilting			
SBP (mm Hg)			
Supine	130 (17)	137 (17)	152 (20)*‡
During tilting	157 (16)*	137 (18)	128 (21)‡
Change	27 (8.9)*	0.50 (8.9)	−24 (6.0)*‡
DBP (mm Hg)			
Supine	71 (11)*	80 (9.6)	83 (10)‡
During tilting	86 (9.7)	83 (11)	79 (16)
Change	15 (6.6)*	3.5 (7.3)	−4.1 (6.0)*‡
PR (beats/min)			
Supine	67 (8.8)	69 (9.6)	65 (8.5)
During tilting	77 (12)	79 (11)	71 (7.8)
Change	9.2 (5.4)	7.1 (5.2)	8.0 (5.4)

Data are shown as the mean (standard deviation) or percentage. *$p < 0.001$; †$p < 0.05$ vs. normal group; ‡$p < 0.001$ vs. orthostatic hypertension group by Tukey's honestly significant difference test after analysis of variance or χ^2 test.

BP = blood pressure; DBP = diastolic blood pressure; ECG-LVH = left ventricular hypertrophy diagnosed by electrocardiography; PR = pulse rate; SBP = systolic blood pressure.

of up to four weeks, and 1 to 5 weeks of maintenance. After the observation period, patients were started on 1 mg of doxazosin daily, taken at bedtime. The dose was doubled at weekly intervals until the following BP reduction had been achieved: the average seated BP had fallen: 1) by >20/10 mm Hg from the baseline level, or 2) by >10/5 mm Hg from the baseline level when baseline BP <160/90 mm Hg. The dose was not increased further if the BP reduction described above was achieved at each of two consecutive visits, or a maximum daily dose of 8 mg of doxazosin had been reached. After the titration phase, there was a maintenance phase of one to five weeks on the same dose of doxazosin. This protocol was modified from that of the Hypertension And Lipid Trial (15,16). The second HUT was performed at the end of the drug-free baseline observation period (three to five weeks) just after the first HUT; and the third was performed at the end of the maintenance period (one to five weeks). The intervals between the first and second HUTs, and between the second and third HUTs, were three to five weeks and four to six weeks, respectively.

Statistical analysis. One-way analysis of variance was performed to evaluate differences among groups, Tukey's honestly significant difference test was used for comparison of the mean values for pairs of groups, and the chi-square test was used to detect among-group differences in prevalence rates. Unpaired *t* tests and paired *t* tests were used for comparison of the mean values for two different groups. Changes of BP or PR from the baseline values were analyzed using paired *t* tests for each group. Adjusted odds ratio (OR) and 95% confidence intervals were calculated using logistic regression analysis. Differences with $p < 0.05$ (two-tailed) were considered statistically significant.

RESULTS

Clinical and BP characteristics. The OHT group was older and showed a greater frequency of ECG-LVH than the ONT group (Table 1) The other characteristics did not differ significantly among the groups, although fewer OHT subjects tended to have previously been on antihypertensive medication when compared with the ONT group ($p = 0.06$). In the HUT, in comparison with the normal group, supine SBP was significantly higher in the OHYPO group, whereas SBP during tilting was higher in the OHT group. No significant differences were seen in the orthostatic PR profiles among the groups.

No significant differences existed in the levels of clinic BPs or ambulatory BPs, except for sleep DBP, among the groups (Table 2). Morning SBP was significantly higher ($p = 0.007$) and morning DBP tended to be higher ($p = 0.09$) in the OHT than in the ONT group. The sleep/awake BP ratio was significantly lower in the OHT than in

Table 2. Ambulatory Blood Pressure Characteristics

Measures	Orthostatic Hypertension (n = 26)	Normal Group (n = 192)	Orthostatic Hypotension (n = 23)
SBP			
Awake (mm Hg)	153 (15)	149 (13)	150 (14)
Sleep (mm Hg)	132 (18)	133 (16)	138 (15)
Morning (mm Hg)	159 (18)†	149 (16)	150 (14)
24 h (mm Hg)	145 (12)	143 (12)	146 (12)
SD of awake SBP (mm Hg)	21 (5.0)*	17 (4.6)	20 (5.2)†
Sleep/awake ratio	0.86 (0.11)	0.89 (0.08)	0.93 (0.10)§
DBP			
Awake (mm Hg)	85 (7.6)	87 (8.6)	86 (8.1)
Sleep (mm Hg)	72 (9.1)‡	77 (9.6)	76 (9.6)
Morning (mm Hg)	93 (6.9)	89 (10)	87 (8.8)
24 h (mm Hg)	80 (6.4)	84 (8.1)	83 (7.7)
SD of awake DBP (mm Hg)	14 (3.8)‡	12 (2.9)	13 (2.3)
Sleep/awake ratio	0.85 (0.09)	0.89 (0.09)	0.91 (0.10)§

Data are shown as the mean (standard deviation [SD]) or percentage.
*$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$ vs. normal group; §$p < 0.05$ vs. orthostatic hypertension group.
DBP = diastolic blood pressure; SBP = systolic blood pressure.

the OHYPO group. Concerning abnormal diurnal BP variation patterns, the extreme-dipping pattern of nocturnal BP (sleep/awake SBP ratio <0.8) was more common in the OHT than in the ONT group (35% vs. 13%, p = 0.004), whereas the nocturnal BP rising pattern (sleep/awake SBP ratio >1.0) was more common in the OHYPO than in the ONT group (26% vs. 9.4%, p = 0.016). The levels and SDs of both awake SBP and DBP were higher in the OHT than in the ONT group. The SD of awake SBP was also higher in OHYPO than in ONT patients.

Silent cerebrovascular disease. The number of SCIs and the prevalence of SCIs were significantly higher in both OHT and OHYPO groups subjects than in the ONT group (Table 3). Advanced DWM lesions were also significantly more common in the OHT than in the ONT group. These associations remained significant after adjusting for demographic characteristics and ambulatory BPs.

Because the definitions of OHT and OHYPO are arbitrary, we next empirically grouped the 241 study patients into quintiles (Q1 to Q5) of orthostatic SBP increase. The ORs for SCI and multiple SCIs after adjusting for demographics and ambulatory BP showed a U-shaped relationship (Fig. 1).

Table 3. Silent Cerebrovascular Disease

Measures	Orthostatic Hypertension (n = 26)	Normal Group (n = 192)	Orthostatic Hypotension (n = 23)
SCI			
Prevalence (%)	81†	48	74
Average number/person	3.4 (2.8)*	1.4 (2.3)	2.7 (2.0)‡
Multiple cerebral infarcts§			
Prevalence (%)	65*	24	65*
Advanced DWM lesion			
Prevalence (%)	62†	31	35

Data are shown as the mean (standard deviation) or percentage.
*$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$ vs. normal group. §Defined as ≥3 silent infarcts (person).
DWM = deep white matter; SCI = silent cerebral infarct.

Neurohumoral factors. The plasma norepinephrine level during tilting was significantly higher (778 vs. 577 pg/ml, p = 0.04) and its orthostatic increase tended to be higher (351 vs. 245 pg/ml, p = 0.06) in the OHT than in the ONT group, whereas the supine norepinephrine tended to be higher in the OHYPO (p = 0.07) group (Table 4). Plasma vasopressin after tilting was higher in the OHT than in the ONT (p = 0.04) and the OHYPO (p = 0.009) groups. The orthostatic vasopressin increase tended to be higher in OHT subjects than in OHYPO subjects (p = 0.06). The orthostatic renin profile was comparable in the three groups.

Reproducibility. The correlation coefficients of the orthostatic BP increases in the first HUT and second HUT were 0.61 for SBPs and 0.47 for DBPs (both $p < 0.001$) in the 55 hypertensives. Of the 13 OHT patients with orthostatic SBP increase of ≥20 mm Hg in the first HUT, 10 (77%) had an orthostatic SBP increase of ≥10 mm Hg, and 5 (38%) had a ≥20 mm Hg increase, in the second HUT.

Effect of alpha-adrenergic blocking. When we defined the OHT on the basis of the average orthostatic SBP increase of the first and second HUTs, 10 patients were classified into the OHT and 45 patients into the ONT group. Figure 2 shows the effect of alpha-adrenergic blocking on orthostatic BP change in each group. In the ONT group, alpha-blocking reduced baseline and orthostatic BPs. In the OHT group, alpha-blocking reduced only orthostatic BP, while baseline BP was not significantly affected. Orthostatic SBP tended to be more markedly reduced in the OHT than in the ONT group (−23 vs. −14 mm Hg, p = 0.09). The orthostatic BP increase was more markedly attenuated in the OHT than in the ONT group ($p < 0.01$).

DISCUSSION

In the present study, we examined asymptomatic hypertensive subjects without previous or currently active cardiovascular disease because the orthostatic BP regulation might be

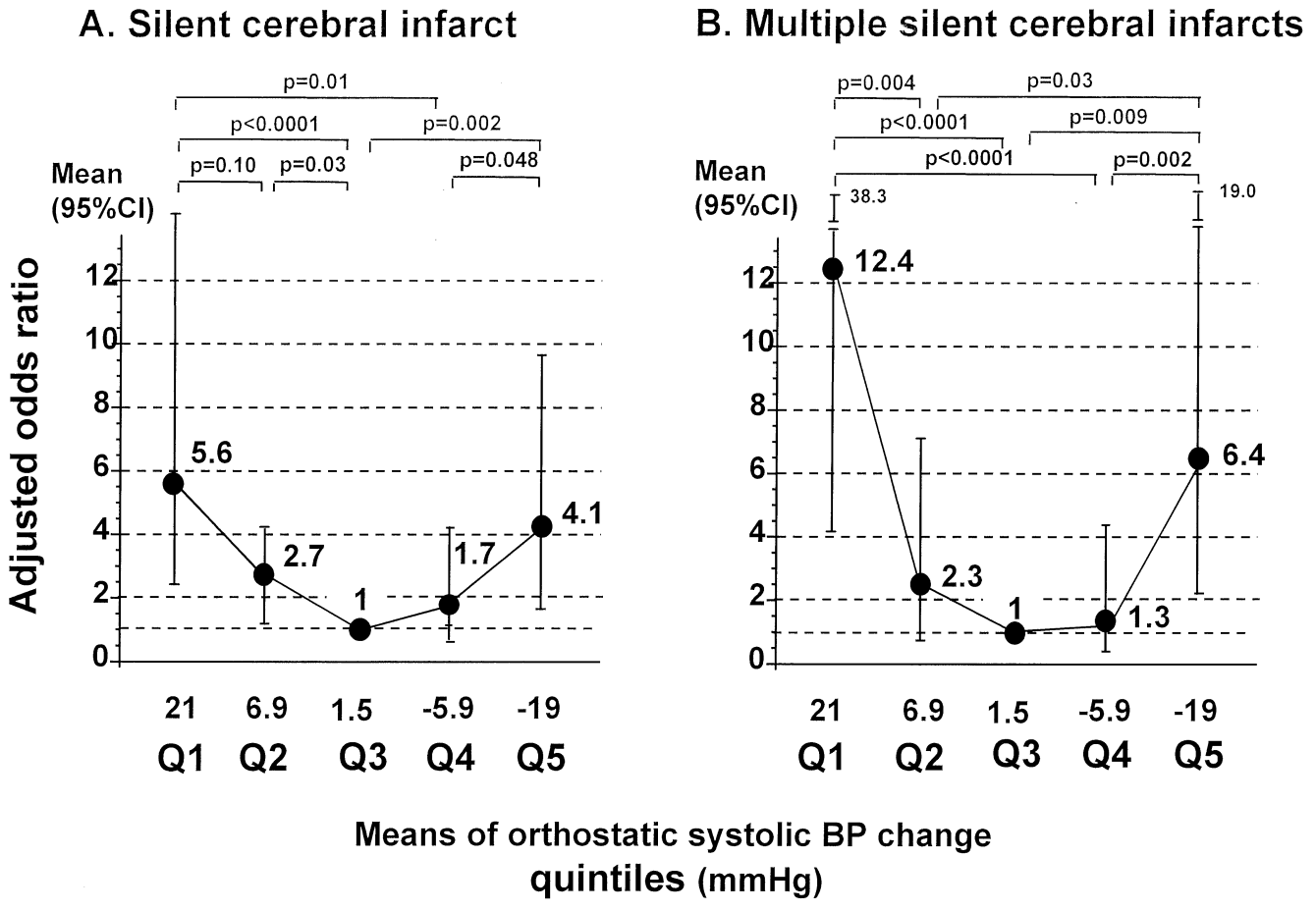

Figure 1. U-curve relationship between orthostatic blood pressure (BP) change and silent cerebral infarcts in elderly subjects with sustained hypertension. The odds ratios (mean and 95% confidence interval [CI]) for silent cerebral infarcts: (**A:** 0 = subjects with no infarct; 1 = subjects with one or more infarcts) or for silent multiple cerebral infarcts (**B:** 0 = subjects with fewer than 3 infarcts; 1 = subjects with three or more infarcts) were adjusted for age (years), gender (0 = female, 1 = male), body mass index (kg/m^2), smoking status (0 = nonsmoker, 1 = current smoker), presence/absence of hyperlipidemia (0 = none, 1 = present), and 24-h systolic BP (mm Hg) using multiple logistic regression analysis (Q3 = the reference group).

altered in patients with overt cardiovascular disease. The prevalence of SCI in elderly hypertensives in this study was 54%, and this value is higher than the values reported in previous studies using brain MRI (41% to 53%) (11,12,17,18), probably due to the exclusion here of white-coat hypertension.

Our main findings were that OHT, as well as OHYPO, is found fairly frequently in elderly Japanese patients with sustained hypertension, and that such patients with OHT have markedly advanced silent cerebrovascular disease. This study provides new evidence indicating that a U-curve relationship exists between orthostatic BP change and hypertensive cerebrovascular disease in the elderly.

Orthostatic BP dysregulation and cerebrovascular disease. The number of SCIs and the prevalence of all silent cerebrovascular diseases (SCI, multiple SCIs and advanced DWM lesion) were significantly higher in the OHT than in the ONT group. Multiple SCIs were more common in the OHYPO than in the ONT group. These associations found in our elderly patients with sustained hypertension were previously also found in community-dwelling Japanese elderly subjects ≥75 years old (8), for whom the mean SCI per person was 3.6 in 10 OHYPO subjects (orthostatic SBP decrease ≥20 mm Hg), and 3.5 in 10 subjects with OHT (orthostatic SBP increase ≥20 mm Hg). These mean numbers of SCIs in both groups were significantly higher than the 2.1 in 20 ONT subjects with orthostatic BP increase of −20 to +20 mm Hg (both $p < 0.05$). In that study (8), posture-dependent BP change was assessed after active standing for 2 min. In the present study, HUT was performed to assess orthostatic BP dysregulation more precisely. Because the definitions of OHT and OHYPO were arbitrary, we empirically grouped the study patients into quintiles of orthostatic SBP increase and found a U-shaped relation between the orthostatic SBP change and silent cerebrovascular disease after controlling for other confounding factors, including ambulatory BP levels. This association was especially marked for multiple SCIs.

There have been no reports showing an association between OHT and cardiovascular events. A recent large population-based prospective study, the Atherosclerosis Risk In Communities study, disclosed that OHYPO is an

Table 4. Neurohumoral Profiles

Measures	Orthostatic Hypertension (n = 16)	Normal Group (n = 66)	Orthostatic Hypotension (n = 5)
Norepinephrine (pg/ml)			
Supine	427 (138)	332 (203)	526 (87)
15-min during tilting	778 (259)*	577 (307)	788 (223)
Orthostatic increase	351 (175)	245 (167)	261 (142)
Epinephrine (pg/ml)			
Supine	30 (17)	31 (29)	42 (21)
15-min during tilting	58 (33)	52 (46)	73 (32)
Orthostatic increase	28 (22)	21 (27)	31 (12)
Renin activity (ng/ml/h)			
Supine	0.50 (0.35)	0.57 (0.55)	0.34 (0.22)
15-min during tilting	0.65 (0.45)	0.85 (0.74)	0.36 (0.18)
Orthostatic increase	0.15 (1.8)	0.28 (0.29)	0.02 (0.08)
Vasopressin (pg/ml)			
Supine	2.2 (1.5)	1.8 (1.1)	1.3 (0.40)
15-min during tilting	3.7 (2.1)*	2.7 (1.3)	1.4 (0.65)†
Orthostatic increase	1.5 (1.6)	0.92 (1.0)	0.13 (0.74)

Data are shown as the mean (standard deviation).
*$p < 0.05$ vs. normal group; †$p < 0.01$ vs. orthostatic hypertension group.

independent risk factor for both stroke (relative risk [RR] = 2.0) (3) and CAD (RR = 3.5) (4). However, that study population consisted of middle-aged subjects, and the association between OHT and cardiovascular events was not examined.

Another prospective study on elderly men >70 years old showed that OHYPO was a risk for total mortality with an RR of 1.64 (2). In that study, a U-curve relationship was not found, but those investigators did not study the cardiovascular events separately. Silent cerebral infarct, which is now classified as a cerebrovascular disorder, type III, by the National Institute of Neurological Disorders and Stroke, has been proposed to be a predisposing condition for subsequent overt stroke. In fact, SCI is a potent predictor of future stroke, with an RR of about 5, in elderly hypertensives (13), and with an RR of about 10 in all adults (19). Thus, OHT may be a risk factor for future clinical stroke in elderly hypertensives.

Mechanism of orthostatic BP dysregulation in silent cerebrovascular disease. The mechanism of the association between orthostatic BP dysregulation (OHT and OHYPO) and silent cerebrovascular disease remains unclear. In addition, whether orthostatic BP dysregulation is a result or cause of silent cerebrovascular disease is not known. The fact that the OHT subjects had a significantly higher frequency of ECG-LVH in addition to being older (two significant cerebrovascular risk factors) may be the reason why they also had advanced silent cerebrovascular disease. In addition, somewhat fewer OHT subjects had previously been on antihypertensive medication, which might have altered baroreceptor response. However, even after controlling for these factors, the association between orthostatic BP dysregulation and silent cerebrovascular disease remained significant.

Autonomic nervous activity may be affected by cerebral infarction (20). Thus, one explanation for the association is that patients with more long-standing hypertension or more severe hypertension suffer greater degrees of silent cerebrovascular disease, leading to autonomic nervous dysfunction and orthostatic BP dysregulation. However, no significant differences existed among the OHT and the other two groups in the hypertension duration, previous antihypertensive therapy or ambulatory BP level. In further support of autonomic dysregulation in patients with OHT, OHYPO and cerebrovascular disease is the observation in Table 2 that BP variability was greater in these groups.

Increased morning BP might have contributed to the increase in the risk for silent cerebrovascular disease in the OHT group. Morning BP increase is reported to be associated with cardiac hypertrophy in hypertensive patients (21), and this may trigger cardiovascular events (22). Theoretically, orthostatic BP increase due to upright position after awakening could partly contribute to ambulatory morning BP. In fact, in our study, morning BP level was significantly higher in the OHT than in the ONT group.

Another possibility is that, particularly in elderly hypertensives with reduced cerebrovascular reserve capacity, frequent episodes of increased BP variability during daily activity might advance silent cerebrovascular disease. In addition, previous studies using brain MRI disclosed that elderly hypertensives with postprandial hypotension (23) and extreme-dipping of nocturnal BP (14) have more advanced hypertensive cerebrovascular disease. In elderly hypertensives, these relative hypotensive conditions (OHT and OHYPO, postprandial hypotension and extreme-dipping of nocturnal BP) increase the ambulatory BP variability, leading to silent and clinically overt cerebrovascular disease (24). In the present study, extreme-dipping status of nocturnal BP was more common in the OHT group, whereas the nocturnal BP rising pattern was more common in the OHYPO group. In addition, ambulatory BP variability (standard deviation of awake SBP) was increased in both the OHT and OHYPO groups compared with the ONT group. A recent prospective study (25) showed that increased postural BP variability is significantly associated with stroke prognosis in elderly nursing home residents. Thus, a hemodynamic mechanism might partly account for the association between orthostatic BP dysregulation and silent cerebrovascular disease in elderly hypertensives.

A recent population-based prospective study demonstrated that men with exaggerated stress-induced SBP response (>20 mm Hg) had 87% greater risk of ischemic stroke than less reactive men (26). Thus, excessive sympathetic reactivity to stress may be etiologically important for silent and clinical hypertensive cerebrovascular disease.

Racial difference. Silent OHYPO in elderly hypertensives (9.5%) is unexpectedly less common among Japanese than in Western populations, where OHYPO is reported to occur in up to 20% to 30% of elderly hypertensives (1). Defined as

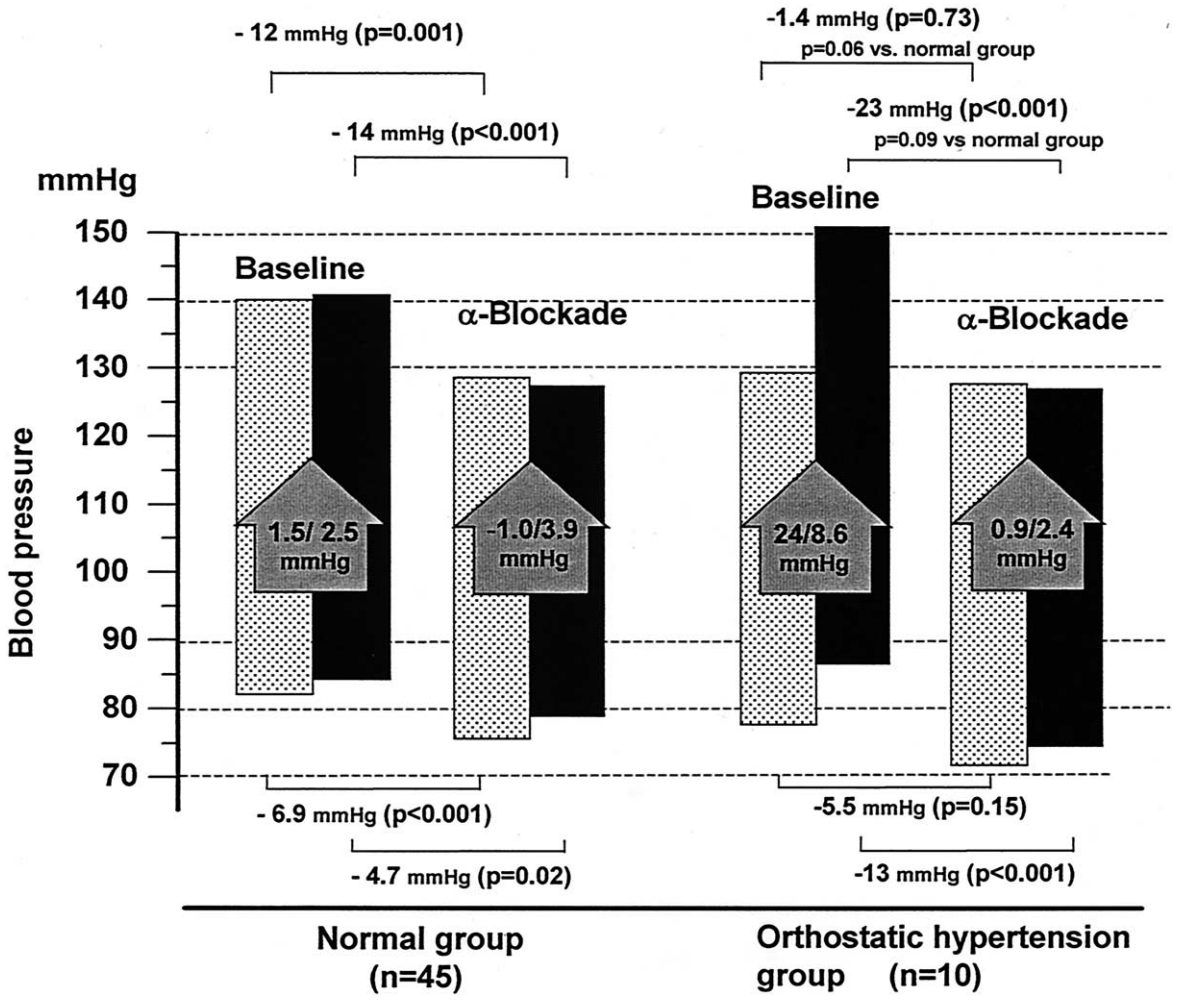

Figure 2. Effect of alpha-adrenergic blocking on orthostatic blood pressure change. The **dotted bars** show the supine blood pressure (**upper edge** = systolic blood pressure; **lower edge** = diastolic blood pressure) and the **solid bars** show the orthostatic blood pressure during tilting test. The **values within the arrows** show the orthostatic blood pressure change (systolic/diastolic) by tilting test. The baseline orthostatic blood pressure increase was significantly higher in the orthostatic hypertension group than in the normal group (systolic blood pressure/diastolic blood pressure: 24/8.6 mm Hg vs. 1.5/2.5 mm Hg, both $p < 0.01$).

an orthostatic SBP increase of ≥20 mm Hg, OHT (11%) is found more frequently than OHYPO among elderly Japanese hypertensives. This orthostatic BP change might reflect a racial difference in the cardiovascular system response between Japanese and Westerners. This speculation may be supported by the finding in a comparative study (27) that, in elderly Japanese individuals, falling occurs at about one-fourth of the incidence in the U.S. This difference might be partly due to the Japanese lifestyle, in which customary squatting behavior would preserve the muscle strength and facilitate venous return from the lower extremities serving to prevent orthostatic BP decrease. All of the elderly subjects we studied engaged in this traditional Japanese form of squatting.

Mechanism of OHT. The mechanism of OHT remains unclear, although some pathogenic processes have been reported (6). Plasma norepinephrine and vasopressin levels during tilting were significantly higher and the orthostatic norepinephrine increase tended to be higher in the OHT than in the ONT group. In addition, morning BP, which was more closely associated with alpha-adrenergic activity than ambulatory BP during other periods (15,28), was increased in the OHT group. The orthostatic BP increase in the OHT group was diminished by alpha-adrenergic blockade. The orthostatic PR profile was comparable among the three groups. These findings suggest that orthostatic activation of sympathetic activation, particularly for alpha-adrenergic activity, might play some role in the pathogenesis of OHT.

The fact that patients with OHT had a higher frequency of ECG-LVH, as well as greater elevation in norepinephrine during tilting, suggests they may have congestive heart failure. A further study using echocardiograms will be necessary to confirm the presence of LVH or quantity the degree of systolic or diastolic ventricular dysfunction in the OHT patients.

Definition and reproducibility of OHT. As various factors affect orthostatic BP change, the reproducibility of OHYPO is relatively poor (29). The reproducibility of OHT when defined

using the cutoff value of 20 mm Hg for orthostatic SBP increase was relatively poor in this study. In addition, the effect of "regression to the mean" may partly explain the observed orthostatic BP change, because the OHT group had the lowest supine BP, and the OHYPO group had the highest.

To minimize the effect of "regression to the mean" in defining OHT and OHYPO, we used the HUT (which measures BP levels every min) instead of the routine active standing test (sitting BP, and BPs 1 min and 3 min after standing). If increased BP variability is the problem with these patients, there will be days when they have supine hypertension and OHYPO and other days when they will have the reverse. Thus, ideally, the classification of OHT and OHYPO groups would have been based on three or more different postural BP measures. However, a significant positive correlation existed between orthostatic BP change in the first HUT and that in a second HUT performed within the following three to five weeks in this study, and no patients with OHT as indicated by the first HUT were classified into the OHYPO group at the second HUT. Thus, one HUT test seems to detect some individual characteristics of orthostatic BP regulation. Conversely, the repeated assessment of routine sitting and standing BP may be more practical for defining the OHT and OHYPO conditions. Further studies focusing on methods and reproducibility will be necessary to establish an adequate definition of OHT.

Study limitations. As this study was cross-sectional, a prospective study will be necessary in the future to strictly address the causality between orthostatic BP dysregulation and silent cerebrovascular disease. There is the possibility that when hypertension causes subclinical cerebrovascular disease in some specific brain area, BP variability increases owing to autonomic nervous system dysfunction. In addition, there was no placebo control arm for our alpha-adrenergic blocking study. Thus, to strengthen our conclusion that alpha-adrenergic hyperactivity is the predominant cause of OHT, a discontinuation study of alpha-adrenergic blockade to confirm the development of OHT again, or a plabebo-controlled study, will be necessary.

Conclusions. Given that elderly hypertensive patients with OHT or OHYPO often have advanced silent cerebrovascular disease, they may be at elevated risk of overt clinical cerebrovascular events. Elderly hypertensive patients should be followed with respect to orthostatic BP changes.

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